

### **III. REMARKS**

#### ***Claim Status***

Claims 1-17 are pending. Claims 1-17 are under current examination.

#### ***Claim Rejections - 35 USC § 112***

Claim 13 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for including the phrase "such as".

The offending language has been deleted, thus obviating this ground for rejection.

Claims 14-15 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement.

Claims 14 and 15 have been cancelled, thus obviating this ground for rejection.

#### ***Claim Rejections - 35 USC § 103***

Claims 1-6 and 9-17 stand rejected under 35 U.S.C. 103(a) as being obvious over Margolskee, USP 5,817,759 in view of Yao et al., USP 7,041,457.

Claim 1 has been amended and is now directed to a G<sub>aq</sub>Gustducin chimeric G-protein where the last 44 amino acids of the G<sub>αq</sub> protein sequence are replaced with a 44 amino acid unit of Gustducin.

Applicant believes this amendment renders moot the current

rejection as neither of Margolskee, nor Yao et al., either alone or in combination disclose or suggest the protein currently claimed by applicant.

Applicant has recognized a problem not known or suggested by the cited references and solved that problem in the novel manner described in the instant specification.

Applicant highlights the problem solved by the instantly claimed invention at page 3 of the specification:

"Thus, since sweet, umami and bitter taste receptors are believed to couple to Gustducin (a  $G_{am}$  type G-protein) and the aforementioned studies suggest that,  $G_{a15}$  and  $G_{a16}$  are not the optimal partners for  $G_{am}$  type GPCRs, a skilled person would not expect efficient coupling of activated taste receptors to either  $G_{a15}$  or  $G_{a16}$ . On the other hand, Gustducin itself does not offer a practical solution as this G-protein modulates release of cyclic nucleotides (cNMPs) which are not as easily measured as, for example, increases in Calcium ions. It is technically difficult to measure cNMPs and requires an immunoassay that generally takes in the order of 4 to 6 hours, and then only provides an end-point assessment. Still further, it is complicated to use a specialized  $G_{ai}$  protein, such as Gustducin in a heterologous cell expression system. To do so, one would have to introduce two additional G-protein sub-units (the beta and gamma sub-units) into the heterologous host cells to fully reconstitute the taste-receptor- G-protein complex.  $G_{a16}$  on the other

hand can complex with beta/gamma sub-units endogenous to mammalian cells, such as cells of the HEK 293 cell line. It is faster, easier and more sensitive to employ  $G_{a16}$  rather than  $G_{a1}$ -type of G-protein such as Gustducin."

The solution to the problem is set forth on page 4 of applicant's specification:

"Surprisingly we have now found that chimeric G-proteins based on  $G_{aq}$ -Gustducin are able to bind to a wide range of known and putative bitter taste receptors, and sweet and umami receptors with high affinity.

Accordingly the invention provides in a first aspect a  $G_{aq}$ -Gustducin chimeric G-protein.

In a specific embodiment the chimeric  $G_{aq}$ -Gustducin is a  $G_{a15}$  or  $16$ -Gustducin protein, more specifically a  $G_{a16}$ -Gustducin protein."

The references do not disclose or suggest the claimed protein. Margolskee does not disclose chimeric proteins. Margolskee merely discloses the known protein Gustducin, in particular the polynucleotide sequences encoding the alpha subunit of Gustducin or fragments of variants.

Margolskee discloses the Gustducin protein and discloses that activation or inhibition of the  $\alpha$  subunit of Gustducin modifies perceived taste. The examiner recognizes that Margolskee does not teach the  $G_{aq}$ -Gustducin chimeric G-protein

and also does not recite replacement of the C-terminal sequence of Gustducin with 5-44 amino acids of the Gustducin receptor.

Yao et al. is cited as teaching various  $G_{aq}$  chimeric G-proteins including  $G_{\alpha q}$  and  $G_{\alpha 15}$  (in mice,  $G_{\alpha 16}$  in humans) and in particular, that the chimeric promiscuous or widely promiscuous Gq proteins described in Yao et al. may have sequences incorporated from other  $G_{\alpha}$  class proteins.

Yao et al. discloses chimeric proteins based on  $G_{\alpha q}$  (in particular, various mouse variants, compare table I) combined with the 5 last amino acids of either transducin or  $G_{\alpha OLF}$ . Yao specifically discloses chimeric proteins based on mouse  $G_{\alpha 15}$  having the last 5 amino acids replaced (several variants).

Yao et al. is also cited as teaching chimeric Gq variants and the isolated nucleic acids encoding the same. In one embodiment disclosed by Yao et al. the chimeric Gq protein variants comprise C-terminal sequences from transducin, which is stated as exhibiting improved functional coupling to taste receptors.

While Yao discusses hypothetical chimeric proteins comprising fragments of up to 44 aminoacids of transducin and  $G_{\alpha olf}$ , it is not clear whether those will work at all. The field is highly unpredictable, and many possibilities of choosing chimeric G-Protein combinations exist. There is no motivation in Yao et al. to choose the 44 amino acid long variant over any other (actually, 5 amino acids are exemplified), nor is there any motivation to choose a particular G-Protein of the various ones that are suggested, which notably excludes gustducin.

The examiner states that Yao et al. further teaches

substituting from 5 to 44 amino acids from the C terminus of transducin or G<sub>aolf</sub>. The examiner therefore concludes that substituting Gustducin for transducin or G<sub>aolf</sub> would be obvious.

Contrary to examiner's remarks, Yao et al. does not mention Gustducin at all, while it does discuss the "gustducin-coupled bitter receptor mT2R5" as a G<sub>aq</sub> variant. Yao does not disclose any chimeric proteins that comprise a 44 amino acid fragment of gustducin.

There is no prior art reference that teaches which parts of which proteins to combine to arrive at a high affinity G-Protein that, thanks to the gustducin-part, couples not only to bitter, but also sweet and umami receptors, thus being a clear advance over the prior art.

Claim 5 is directed to an amino acid set forth in claim SEQ ID NO:2. The examiner is interpreting the claim to mean that a subsequence of SEQ ID NO:2 could satisfy the limitations of the claim. Therefore, the teachings of Margolskee satisfy this limitation.

Claim 5 has been amended to claim the sequence of SEQ IS NO:2 and not subsequences thus obviating this ground for rejection.

Claim 6 is directed to a nucleic acid encoding the G-protein of claim 1. The examiner is interpreting the claim to mean that a subsequence of SEQ ID NO:1 could satisfy the limitations of the claim and concludes that the teachings of Margolskee satisfy this limitation.

Claim 6 has been amended to claim the sequence of SEQ ID NO:1 and not subsequences thus obviating this ground for rejection.

Claim 9 is directed to a host cell transformed with the expression vector of claim 8. The examiner states that Margolskee teaches stably transformed host cells comprising the expression vector.

Applicant traverses this ground for rejection. Applicant is claiming specific stably transformed host cells comprising the expression vector, which transformed cells are novel and have a superior utility.

Claim 10 is directed to methods of producing a chimeric G-protein of claim 1 by recombinant technology. The examiner states that Margolskee teaches, "large scale production of gustducin  $\alpha$  subunit polypeptides" by recombinant methods.

Applicant traverses this ground for rejection. Applicant is not merely producing any chimeric protein or any chimeric G protein. Applicant is claiming very specific G proteins not disclosed or suggested by the prior art. That chimeric proteins in general can be produced by large scale methods is not being claimed by applicant.

Claim 11 is directed to a method of analysis and discovery of modulators of bitter taste receptors using the chimeric proteins of claim 1.

The examiner cites Margolskee as teaching, "methods for identifying taste modifying agents having the capability to affect interactions between the gustducin  $\alpha$  subunit and taste

receptors or effectors and also describes methods for utilizing such taste modifying agents to modify taste by mimicking or inhibiting...bitter." (col. 4, lines 52-56).

Applicant traverses this ground for rejection. As stated above, Margolskee is describing a different process in that he is not utilizing the chimeric proteins of claim 1 - and therefore is not obtaining the benefits of the improvement claimed by applicants.

Claims 12-13 are directed to a method of claim 11, wherein the assay is a mammalian cell-based assay. The examiner cites Margolskee as teaching, such mammalian cell-based assays that measure changes in intracellular messengers, including phosphodiesterase which affects  $\text{Ca}^{2+}$  and IP3 production.

Applicant traverses this ground for rejection. As stated above, Margolskee is describing a different assay in that he is not utilizing the chimeric proteins of claim 1 - and therefore is not obtaining the benefits of the improvement claimed by applicants

Claims 14-15 have been cancelled.

Claims 16-17 have been cancelled.

In conclusion, the combination of Margolskee with Yao does not arrive at the present invention. Margolskee is not related to chimeric proteins at all, but merely discloses the known protein Gustducin, and therefore is of no help.

There is no prior art reference that teaches which parts of which proteins to combine to arrive at a high affinity G-Protein that, thanks to the gustducin-part, couples not only to bitter, but also sweet and umami receptors, thus being a clear advance over the prior art.

***Allowable Subject Matter***

Claims 7-8 stand objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Please charge any insufficiency of fees, or credit any excess, to Deposit Account No. 14-1263.

Respectfully submitted,

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